Rise of Gluten Intolerance Begins at Birth: Effects of Infant Feeding on Celiac Disease

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Abstract: *Celiac disease (CD), a disorder marked by intolerance to the protein gluten, appears to have increased in the world's population over the past fifty years, afflicting a mere 0.03% in the 1970s, and almost 1% today. It has been argued that this observed rise is simply due to more advanced screening techniques that diagnose more cases of CD, though the disorder is just as common now as it has always been. However, numerous studies have proven this hypothesis incorrect, illustrating that celiac disease is indeed becoming more common. This massive jump in the prevalence of CD must have an underlying cause, such as a change in human lifestyle since the 1970s. Research suggests that changes in the population's methods of feeding infants, specifically breastfeeding, are the forces propelling the CD epidemic. Although studies thus far have illustrated a relationship between celiac disease and the many aspects of infant feeding, more research on the topic should be done in order to determine whether or not the relationship between CD and infant feeding applies for all methods of infant feeding, and if these methods have changed since the 1970s.*

Introduction

Celiac disease is an autoimmune disorder characterized by intolerance to gluten, a protein found in wheat, barley, rye and some other grains. Science writer Moises Velasquez-Manoff explains in "Who Has the Guts for Gluten?" that in individuals with the disease, exposure to gluten causes the "body to turn on itself and attack the small intestine" (1). The telltale signs of celiac disease are the presence of anti-gluten particles in the bloodstream, called antibodies, and villous atrophy, or the inflammation of small finger-like projections in the small intestine, called villi. When an individual has CD, they are less able to absorb nutrients in the small intestine; the disease can be manifested through a variety of signs and symptoms. These symptoms include short stature, bloating, vomiting, fatigue, diarrhea, and irritability (Johnson 1).

In their article, "Increasing prevalence of celiac disease over time," researcher S. Lohi and colleagues recognize that although celiac disease afflicted a mere 0.03 percent of the world's population in the late 1970s, its prevalence has risen to an astonishing 1.0 percent in the United States and Europe in just under fifty years (1218). This indicates that the disease has likely risen across the globe. In fact, the prevalence of CD is predicted to range from 0.6 percent to 1.0 percent worldwide today (Velasquez-Manoff 1). Though these cases of CD may not be distributed uniformly around the globe, the rise of the average rate worldwide will be examined. What is the cause for the drastic increase in the number of cases of celiac disease since the late 1970s? One hypothesis for this increase, which will be called Hypothesis 1, is that knowledge about gluten intolerance has increased, and screening methods for the disease have become more advanced over time; thus, the prevalence of celiac disease is the same as it has always been, but today we are more able to recognize and diagnose it. Conversely, another hypothesis states that celiac disease has actually been plaguing the population more and more as time goes on. This hypothesis will be referred to as Hypothesis 2. Research in the area of celiac disease supports the latter hypothesis, providing statistics of higher levels of celiac-positive patients today. If this hypothesis is correct, there must be an explanation underlying the increased prevalence, perhaps an environmental or genetic factor that has emerged since the late 1970s.

If the observed rise in celiac disease over the years is due to an actual increase in CD prevalence, it is necessary to question the factors responsible for such a propelling increase. William Davis, M.D. and author of *Wheat Belly*, hypothesizes that the rise of CD is due to the fact that wheat has been genetically modified over the past few decades to contain more gluten, thus more easily triggering the body's immune response. This premise has been strongly criticized because gluten itself is not the cause of celiac disease. Therefore, an increase of gluten content in food products would not cause more people to obtain CD but would merely cause their symptoms to appear after eating a smaller quantity of wheat. Further research on the factors responsible for the increase in CD, show an

overwhelming amount of evidence that links an individual's risk of celiac disease to the methods by which he or she was fed as an infant. Dr. Anneli Ivarsson and colleagues claim in "Prevalence of childhood celiac disease and changes in infant feeding" that change in infant feeding methods is an environmental factor that strongly corresponds with the increase in celiac disease (1). The observed rise in the prevalence of CD since the late 1970s is most likely a reflection of an actual increase in its prevalence and the surge can be explained by the change in breastfeeding methods since the 1970s. The apparent relationship between CD and age of gluten introduction suggests that the age that gluten is introduced has changed since the 70s and also contributes to this increase.

The Basis of Hypothesis One

Celiac disease is becoming gradually understood over time. The article "Ages of celiac disease: from changing environment to improved diagnostics" notes that since the end of the seventeenth century, Greek physician Aretaeus of Cappadocia recognized celiac disease in his patients (Tommassini 1). Despite this recognition, knowledge about CD remained minimal until 1950, when Dutch pediatrician Willem Karel Dicke successfully determined that patients with celiac disease could be treated with a diet free of wheat and rye flours. He had not yet understood that this treatment was successful, largely because it removed the protein gluten from the diets of patients'. This information was determined two years later by Australian pediatrician Charlotte Anderson. Scientific celiac disease testing became possible in 1964, when antigliadin antibodies (AGA), which are the body's defense mechanism against gluten and represent gluten intolerance, were identified and able to be detected through an assay (2). An assay is a laboratory test that detects the presence of a target particle, such as an antibody, in a substance such as blood. Now that physicians had a definite indicator of the disease, they could correctly identify more cases of celiac than ever before. Tommasini and colleagues state that the development of the AGA assay proved that "intolerance to gluten was in fact more frequent than previously expected" (2). This concept directly supports Hypothesis 1.

By the 1990s, more indicators of celiac disease, such as antiendomysium antibodies (AEA) and anti-type-2-transglutaminase antibodies, were identified (2). With all of these new avenues for celiac disease detection, it is logical that physicians were able to recognize more cases of celiac than before this information surfaced. Christina Frangou's article, "Gluten Sensitivity Baffles Celiac Disease Specialists" notes that physicians' understanding of celiac disease continually increased until today, stating:

> Fifteen years ago…even gastroenterologists had a poor understanding of gluten and celiac disease…Misconceptions included theories that only children and adults of northern European descent developed celiac disease, and that the symptoms…were evident only in the gastrointestinal (GI) tract…'We now know that…every ethnicity is at risk and that most frequently these people present with symptoms that have nothing to do with the GI tract,' said Dr. Fasano. (3)

Considering the progress that has been made in the medical community since the late 1970s, the hypothesis favoring medical advancement as the cause of increased CD prevalence seems valid. On the contrary, further studies conducted to settle the debate between the two hypotheses prove this argument invalid.

Hypothesis Two Reigns Supreme

Lohi and colleagues set out to determine whether or not celiac disease was actually on the rise, recognizing that "the changed prevalence figures have sparked off debate as to whether the increasing prevalence of the condition reflects a true rise in prevalence in the course of time or whether it is due simply to the better detection rate" (1218). They set up an experiment in which they examined a sample of 8,000 Finnish adults in 1978-80, and 8,028 Finnish adults in 2000-01. The adults from both groups answered a questionnaire about their health, as well as providing a blood sample. The researchers then took the samples of each individual's blood and tested them for AEA, which indicated the prevalence of celiac disease. The blood samples of the 1978 to 1980 test group were frozen, and both groups were analyzed after the 2000 to 2001 test group was studied. Both blood samples were examined using the same screening

method, thus, removing the bias that may be caused by the advancement in medical technology over the years. The researchers totaled the amount of individuals whose blood samples contained AEA antibodies; these individuals had celiac disease. After comparing the total number of cases of CD in the 1978 to 1980 group with that of the 2000 to 2001 group, the study found that celiac disease was significantly more prevalent in the latter (1218-1221). These results explicitly illustrate that the prevalence of celiac disease is increasing with time. The researchers used the same screening method to survey the samples, so the discrepancy between the prevalence of AEA cannot be a result of more advanced medical technology, therefore discrediting Hypothesis 1. Lohi and colleagues explain that the prevalence of CD "almost doubled during the time span examined, being 1.05 percent in 1978-80 and 1.99 percent in 2000-01" (1221). This group of researchers began their experiment with an open mind as to the cause of the observed increase in the disease; their findings allowed them to confidently dismiss the argument for more advanced screening techniques.

This experiment is one of many that support the hypothesis of increased Celiac Disease over time. For example, Velasquez-Manoff's article states, "[Scientists] have analyzed serum stored since the mid-20th century and compared it to serum of Americans today. Today's serum is four times as likely to carry those antibodies" (2). These findings are even more indicative of the validity of Hypothesis 2, since they compare today's population with a population dated a century ago. If Hypothesis 1 were correct, the prevalence of CD would be nearly equal in two populations, regardless of the size of the time period between the two. Hypothesis 2 is supported by many studies such as the two cited above, and can be confirmed as the correct explanation for the observed increase in celiac disease. However, while there is now an awareness of the rapidly rising percentage of individuals with the disorder, the cause for this surge must be identified.

Infant Feeding Drives the Rise of CD

Upon the emergence of findings that support Hypothesis 2, researchers began to brainstorm about the cause behind this increase of

CD. The scientific community considered both environmental factors and genetic factors to be the potential cause of this increase. However, Velasquez-Manoff provides insight into the likely force behind the rise in celiac disease (4) when he expresses, "an 'epidemic' of celiac disease that struck Sweden some 30 years ago." This sudden increase in Sweden parallels the more gradual increase of celiac around the world, and therefore provides important data on which researchers can base their new predictions. As scientists began to examine the Swedish epidemic, they discovered that:

> Just before the spike, official guidelines on infant feeding had changed. In an effort to prevent celiac disease, paradoxically, parents were instructed to delay the introduction of gluten until their babies were six months old. That also happened to be when many Swedish mothers weaned their children [off of breastfeeding]…The epidemic ebbed only when authorities again revised infant-feeding guidelines. (4)

These findings show that the prevalence of CD changed significantly due to the timing of the changes in infant feeding guidelines, indicating that infant feeding has an impact on the risk of developing celiac. Because this epidemic was most likely caused by the changes in Sweden's infant feeding guidelines, it can be assumed that the first revision of the guidelines provoked celiac disease. Therefore, the introduction of foods containing gluten, such as wheat-based cereals, into the infant's diet at six months old combined with the cessation of breastfeeding is a recipe for the increase of celiac disease. The second time Sweden revised their guidelines, they suggested that mothers "keep breastfeeding…while simultaneously introducing small amounts of gluten" (4). Because these guidelines coincided with the end of the celiac epidemic, breastfeeding must be pertinent to a child's development of tolerance for gluten. While the correlation between the rise in celiac disease and the change in infant feeding recommendations provides promising evidence, further study of the Swedish epidemic is necessary in order to reach a feasible conclusion about the relationship between infant feeding and CD.

In their study titled "Prevalence of childhood celiac disease and changes in infant feeding," Dr. Anneli Ivarsson and colleagues tested whether or not infant feeding was actually responsible for the Swedish epidemic. They took a group of 12-year-olds born during the epidemic and tallied the number of participants who had CD, while also surveying their families about how they were fed as infants. The families logged information such as the age at introduction to gluten and whether or not breastfeeding was still taking place at that time. Later, Ivarsson and colleagues studied a group of 12-year-olds born after the epidemic using the same methods they used for the first group. Their results showed that the group of children born during the epidemic had a higher occurrence of celiac disease, and displayed a lower percentage of breastfed children at the age of gluten introduction (2-4). In other words, children who were introduced to gluten-containing foods during ongoing breastfeeding had the lowest risk of developing celiac disease. The results of this experiment strongly suggest breastfeeding as a force against gluten intolerance. The article "Effect of breast feeding on risk of coeliac disease: a systematic review and meta-analysis of observational studies" by Akobeng and colleagues yielded very similar results. Ivarsson and colleagues scratch the surface regarding the reason behind this phenomenon, offering, "introducing gluten during ongoing breastfeeding may increase the chance of developing oral tolerance through immune-modulating factors in breast milk" (7); this phenomenon will be further explained below. Ivarsson and colleagues, like Velasquez-Manoff, conclude that breastfeeding plays a prominent role in reducing the risk of celiac disease. Though they do not provide further research to specify the exact role of breastfeeding, these studies open the door to further research on the subject.

Effects of Breastfeeding on Celiac Disease

Perhaps influenced by the examination of the Swedish celiac disease epidemic, Dr. Yolanda Sanz pinpointed exactly why breastfeeding is key to preventing celiac disease. She discovered that "a group of bacteria native to the intestine known as bifidobacteria were relatively depleted in children with celiac disease compared with healthy controls" (Velasquez-Manoff 3). This finding shows that a low number of bifidobacteria is

present in individuals with celiac disease. Dr. Sanz then noted that bifidobacteria switched the response of human intestinal cells to gluten from inflammation to tolerance (3). Bifidobacteria, when present in the intestine, prevent the body from reacting to gluten, therefore creating tolerance to gluten. Breastfeeding is so important in the prevention of celiac disease because "bifidobacteria occur naturally in breast milk… breastfed infants tend to harbor more bifidobacteria than formula-fed ones" (3-4). Because breastfeeding supplies an infant with bifidobacteria, the breastfeeding process is essentially one that creates a tolerance to gluten. Therefore, if an infant is breastfed during the same time period as he or she is introduced to gluten, the infant will tolerate gluten much more than if breastfeeding was not taking place.

If breastfeeding does, in fact, lower an individual's risk of developing CD, as illustrated above, then the celiac epidemic could have been caused by a change in breastfeeding rates since the 1970s. In 1995, Grummer-Strawn surveyed mothers from fifteen developing countries around the world to document the amount of time that they had breastfed their child. These results were then compared to similar surveys from the late 1970s and the late 1980s. The study found that "changes in the characteristics of the population have almost universally pushed breastfeeding durations in a downward direction" (Grummer-Strawn 94). Because mothers have been breastfeeding their children for less and less time since the 1970s, the amount of children receiving bifidobacteria throughout the time when they are introduced to gluten has declined. This trend would indeed cause an increased risk of celiac disease in these fifteen developing countries. Although these countries cannot represent the world as a whole, the downward trend of breastfeeding in these areas can be a contribution to the overall 0.6 percent increase of CD worldwide. The article explains that the reasons breastfeeding had decreased from 1970 to 1995 are because of "Patterns of urbanization, improving education levels, increases in contraceptive use, and changing patterns of childbearing" (100). These countries' suggested decreased reliance on breastfeeding corresponds strongly with the rise of CD around the world, and appears as a strong candidate for one of the forces behind the epidemic.

Effects of Age at Gluten Introduction on Celiac Disease

After studying the findings of Ivarsson and colleagues regarding the role of breastfeeding in decreasing a child's risk of celiac disease, Jill Norris and colleagues acknowledge in their article, "Risk of Celiac Disease Autoimmunity and Timing of Gluten Introduction in the Diet of Infants at Increased Risk of Disease," that an infant diet must have the potential to strongly affect the infant's risk of celiac disease. In order to examine other aspects of an infant diet relative to celiac, Norris and colleagues decided to study the impact of an infant's age at gluten introduction on their risk of developing the disease. They performed an observational study from 1994-2004 on babies at high risk for developing celiac disease. High-risk level was characterized by having family members with celiac disease, or gene alleles that predisposed them to celiac disease. The parents of the babies at 3, 6, 9, 12, and 15 months of age were interviewed in detail about their child's feeding habits. The parents were asked specific questions about what types of food were fed to the child and on what date the food was introduced or discontinued. The babies also had their blood drawn at these examinations. The blood was tested for celiac disease, which was defined as the presence of tissue transglutaminase (tTG) antibodies in the bloodstream. After this period of time, the children had their blood drawn at 3-6 month intervals. The study found that children who had gluten introduced into their diet, before 3 and after 7 months of age, were more likely to develop celiac disease than the babies who were introduced to gluten at 4-6 months of age (2344-2349). This study defines an ideal range in which infants should be introduced to gluten. The findings of Norris and colleagues indicate that the age of an infant at gluten introduction has an impact on the risk of celiac disease. However, the role of age at gluten introduction in the rise of celiac disease cannot be determined until the trend of this infant feeding method since the 1970s is surveyed.

To account for the infants' higher risk of developing celiac disease after age seven months, Norris and colleagues recognize that "infants first exposed to cereals at or after the seventh month were more likely to

have been given 1 or more servings per day in the first month of exposure compared with children who were first exposed before 4 months" (2349). Because older infants were initially exposed to gluten more frequently than younger infants initially exposed to gluten, it can be hypothesized that large amounts of gluten upon introduction increase risk of developing celiac. This finding supports Ivarsson and colleagues' prediction that "small amounts" of gluten upon introduction yield the best results for infants. In order to determine the distinct relationship between amount of gluten at introduction and CD, further research is necessary.

Infant Feeding Methods and CD Symptomology

While it has been made apparent that infant feeding techniques have had a strong impact on the change in prevalence of celiac disease, they also seem to have an effect on the signs and symptoms of CD. Though many celiac cases present with similar signs and symptoms such as villous atrophy, Frangou states,

> 'Villous atrophy is just the tip of the celiac disease iceberg…' Stephen Wangen…chief medical director and founder of the Center for Food Allergies in Seattle…said. Up to 130 different symptoms are associated with gluten sensitivity, and virtually every tissue in the body can be affected. (3)

Evidently, celiac disease manifests itself in many different ways, and each individual experiences a symptom, or symptoms unique to his or her case. Astoundingly, Dr. Michael D'Amico and colleagues found that breastfeeding patterns and age at gluten introduction have some influence on the symptoms that appear in a child's case of CD. They state in their article, "Presentation of Pediatric Celiac Disease in the United States: Prominent Effect of Breastfeeding," "When compared to children who were formula-fed exclusively, [exclusively breast fed] children were significantly less likely to report failure to thrive (69% vs 88%), short stature (37% vs 62%) and vomiting (24% vs 52%)" (253). These three symptoms are very common in celiac patients; failure to thrive refers to an inability of the child to grow and gain weight according to childhood norms, which may be a result of vomiting and may lead to short stature.

As previously noted, breast milk provides infants with

bifidobacteria, which promotes gluten tolerance. If infants are receiving breast milk as their sole form of nutrition, they are taking in a maximum amount of bifidobacteria; the results of D'Amico and colleagues' study suggest that maximizing the intake of breast milk ameliorates some of the unpleasant symptoms of CD. In addition, the study found that "Respondents introduced to wheat before 6 months of age were significantly more likely to exhibit failure to thrive before diagnosis ($p<0.1$) than those with a later introduction" (254). This statistic shows that the child's age at gluten introduction also has an effect on the risk of failure to thrive. While this time frame of gluten introduction does not line up with the 4-6 month window suggested in Norris and colleagues' study, it does recognize the effect of this infant feeding method on CD symptoms. From these results, it can be deduced that the further along a child is introduced to gluten, the less likely it is that child will suffer from failure to thrive, if he or she develops celiac disease. Thus, breastfeeding and gluten introduction have the power to increase a child's risk of developing celiac disease and may determine the severity of the symptoms from which they will suffer.

Conclusion

Although celiac disease was seemingly once a medical mystery, knowledge about this condition has increased dramatically over the past few decades. Coincidentally, studies have shown that, despite debate in the medical field, the rate of CD in the worldwide population has increased as well. Many hypotheses have been offered to explain the apparent rise in the prevalence of celiac disease, including claims of higher gluten content in wheat products. However, countless studies on the effects of infant feeding on the prevalence of CD have provided striking evidence for infant feeding as the force behind the upward trend of the disease. Moreover, breastfeeding and age at gluten introduction coincide so strongly with the risk of celiac disease that they have been shown to affect the symptoms and the severity with which the condition appears. Because breastfeeding has a strong relationship with celiac disease, the decline in the duration of breastfeeding since the 1970s provides evidence that breastfeeding is one force behind the CD rise. Age of gluten introduction is another method

of infant feeding that has an effect on CD; however, no research has been done thus far to measure whether or not the world's common age of gluten introduction has changed. Age of gluten introduction cannot be faulted as increasing the rate of CD since the 1970s until more research is done on the topic. Research suggests that at least one aspect of infant feeding has propelled the disease. With further research on the changes of infant feeding from the 1970s to the present, specifically in regards to the amount of gluten at introduction, more scientific evidence will be able to enhance the understanding of the increased prevalence of celiac disease. With the body of evidence supporting infant feeding as the control panel of the disease, we may begin taking steps toward the perfect formula for lifelong tolerance of gluten.

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